ORIGINAL ARTICLES

SULFANILAMIDE AND SULFAPYRIDIN IN THE TREATMENT OF VARIOUS INFECTIONS*

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PART I

THE use of sulfanilamide and sulfapyridin in the treatment of a variety of infections has stimulated and excited tremendous interest within the past three years. Of these two drugs, sulfanilamide has had a much wider use than sulfapyridin, and we are just beginning to learn more about the value of sulfapyridin in the treatment of such infections as those due to the pneumococcus.

Today, I propose reviewing briefly our own experience with these two drugs; and since the time at my disposal is limited, I will summarize our results without presenting the details of cases. In order to synopsize the results of the use of sulfanilamide so far, I have made Table 1. This is, of course, only tentative and cannot be taken to be final, since additional experience may necessitate a change in our views, especially with reference to certain diseases.

TABLE 1.—*On Use of Sulfanilamide*

Diseases in Which Sulfanilamide Has a Proved Value:
1. Streptococcic infections
2. Meningococcic infections
3. Gonococcic infections
4. Urinary tract infections due to B. coli, B. influenzae, B. proteus, Staphylococcus aureus
5. Pneumococcic meningitis
6. Experimental malaria

Diseases in Which Sulfanilamide Is of Suggestive Value:
(Experience too limited or results not conclusive)
1. Undulant fever
2. Pylephlebitis suppurativa
3. Trachoma
4. Lymphogranuloma inguinale
5. Chancroid
6. Actinomycosis
7. Typhoid fever and paratyphoid fever

Diseases in Which Sulfanilamide Is Ineffective:
1. Subacute bacterial endocarditis
2. Staphylococcic infections
3. Rheumatic fever
4. Influencing the rash of scarlet fever
5. Preventing a recrudescence of rheumatic fever following hemolytic streptococcic infection
6. Sterilizing local foci of hemolytic streptococcic infection

Diseases in Which Sulfanilamide Has Been Used Prophylactically:
1. Preventing hemolytic streptococcic infection in rheumatic subjects, and in pregnant women who are about to go into labor.

In assessing the value of any therapeutic agent in the treatment of infectious diseases, two general methods can be used. It can be ascertained whether the fatality rate is decreased, or it can be determined whether the total duration of the disease is shortened, the natural history of the disease changed, or complications prevented. When the fatality rate is high or the disease is self-limited in duration, then the problem is much easier than when one is dealing with a disease in which the fatality rate is low and the disease is indeterminate in duration.

Of the diseases in which there seems to be little doubt about the beneficial effects of the drug, those due to the hemolytic streptococcus, the meningococcus, the gonococcus, and certain organisms causing urinary tract infections are most important and require comment.

STREPTOCOCCIC INFECTIONS

It now seems clear that sulfanilamide reduces the fatality rate in cases of hemolytic streptococcic bacteremia, in puerperal sepsis, and in meningitis.[1] It reduces the total duration of the disease process in cases of erysipelas and cellulitis, and it aids in the sterilization of empyemata due to the hemolytic streptococcus. In hemolytic streptococcic pneumonia its effect is uncertain, since there are too few cases on record to allow one to make a decision. The results in the treatment of tonsillitis and scarlet fever have been somewhat difficult to assess. The total duration of the disease does not seem to be shortened, and sulfanilamide does not affect the rash of scarlet fever. In some reports, the total number of complications in treated cases has been small, whereas in others this feature has not been so striking. When otitis media, due to the hemolytic streptococcus, is present, sulfanilamide apparently decreases the number of cases of acute mastoiditis requiring operation.

In general, the drug has been ineffective in subacute bacterial endocarditis, although there are isolated observations here and there throughout the country in which recoveries or, at least, remissions of long duration have been observed. It has also been found ineffective in preventing recrudescences of rheumatic fever following streptococcic infection, and it is of no value in the treatment of rheumatic fever.

In the prevention of sore throat in rheumatic subjects, several groups of investigators have given the drug in small daily doses for over a year, with encouraging results. It has also been recommended in the prevention of puerperal sepsis in pregnant women who are about to go into labor.

It would appear that sulfanilamide acts in these cases by (1) inhibiting the growth of the organism, (2) actually killing some strains in small numbers, and (3) prolonging life until an infection is localized, and finally destroyed, by the immune processes of the body. In order to accomplish this, it is necessary to have a high concentration (at least 7 to 10 milligrams per 100 cubic centimeters) of the drug in contact with the organisms and an active immune process.

MENINGOCOCCIC INFECTIONS

Following the demonstration that sulfanilamide prevented death from meningococcic infection in mice,[2] and in view of the fact that the drug inhibited

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the growth of the organism *in vitro,* it has been used in a large number of cases of meningococcic meningitis in man. The results of this type of treatment have been most encouraging when used either alone or in combination with specific serum. In brief, it has been shown that the fatality rate can be reduced to between 10 and 15 per cent, the spinal fluid is often sterilized within twenty-four hours of its administration, and the total duration of the disease is shortened. Inasmuch as the drug diffuses rapidly into the cerebrospinal fluid when taken by mouth, it is unnecessary to give the drug intrathecally. It is necessary, however, to maintain the concentration of the drug in the spinal fluid in the neighborhood of 8 to 10 milligrams per cent. All samples of spinal fluid should be examined for (1) the presence of organisms, (2) the level of sulfanilamide, (3) the number of cells, and, when available, (4) the total sugar content. The drug should be given by mouth every four hours and, if necessary, by nasal catheter rather than by hypodermoclysis. If it is necessary to give it by hypodermoclysis, the drug should be given every four hours, 1 gram in 125 cubic centimeters of distilled water or salt solution. While it would be premature to say that this form of treatment is as effective as specific serum, the results so far reported indicate that this is the case. The best method to adopt for the present would seem to be the use of sulfanilamide alone at the beginning of the treatment and, if one fails to sterilize the spinal fluid within twenty-four hours, then it may be necessary to give specific serum. Lumbar punctures should be done every twelve hours until the fluid is sterile, and then every twenty-four hours until it is normal.

Cases of chronic meningococcemia will also respond in a satisfactory way to this drug.

GONOCOCCIC INFECTIONS

Numerous cases of gonococcic infections, including infections of the genital tract, the eyes, and the joints, have been treated with sulfanilamide with varying results. Our experience[3] with the use of the drug *in vitro* showed that the gonococcus was inhibited in its growth when the concentration of the drug was 5 milligrams per 100 cubic centimeters or higher. In the case of many strains the organisms were actually killed in this concentration. From clinical experience with the drug, one can say that, as far as urethritis is concerned, the cases can be divided into three main categories: (1) Those in which the urethritis is cured within a period of seven days. This represents about 50 per cent of the cases. (2) Those in which the signs of acute urethritis subside promptly but the patients continue to carry organisms in the urethra. This is a most important group, since the patient may continue to be a source of infection and cannot be pronounced cured until all the organisms disappear from the genital tract as proved by culture. (3) A group of patients whose course seems to be unaffected by the drug. In some of these patients, the drug seems to be more effective later in the course of the disease than it does in the early stages of the infection.

In the cases of arthritis,[4] it can be shown that infected synovial fluid can be sterilized within several days after the drug is administered, provided the concentration of sulfanilamide in the synovial fluid is 5 or more milligrams per 100 cubic centimeters. It is in this group of cases that the most striking clinical results are obtained. Less striking results may be seen in the patients with noninfected synovial fluid, but even in this group the total duration of the disease is shortened. Recurrences of the arthritis, fever, and urethritis may follow the withdrawal of the drug, so that it is well to continue its use until all signs of infection have disappeared. There is some evidence that the body defense mechanism is of importance in ridding the body of organisms.

Very striking results have been obtained in the treatment of gonococcic ophthalmia; in the few cases that I have seen the results have been most impressive. It has been found by Michels[5] and others that there is a rapid decrease in the edema and discharge, with a sterilization of the exudate and a great reduction of the number of days of hospitalization. In the series reported by Michels, the reduction of hospitalization from 28.5 days in a control series to 5.8 days in a treated series was very striking.

In short, it can be said that sulfanilamide is one of the most effective drugs available at present for the treatment of gonococcic infections and, while other methods of treatment are necessary in many cases, it should be given an adequate trial in all.

URINARY TRACT INFECTIONS

There is general agreement that urinary tract infections due to B. coli, B. proteus, Staphylococcus aureus, and B. influenzae are favorably influenced by sulfanilamide. Bliss and Long[6] have reported failure in infections due to Group D streptococci, and Helmholz[7] has not observed favorable results in those with Streptococcus faecalis. There is no doubt that sulfanilamide exerts a measurable bacteriostatic effect in urine and in clinical cases it has been found effective even when the urine is alkaline. As one studies these infections of the urinary tract in adults, it becomes evident that the drug inhibits the growth of organisms so that, in some cases, there is complete sterilization of the urine. In others, the organisms disappear during the administration of the drug, but reappear when it is discontinued. We have found it of value in pyelonephritis of pregnancy, in chronic bacilluria and cystitis, and in individuals with pyelonephritis without obstruction in the urinary tract. The most conspicuous results have been obtained with B. coli infections, and the best results are obtained when the urine contains at least 100 milligrams of free sulfanilamide per 100 cubic centimeters. This can usually be accomplished by giving 2 or 3 grams a day and restricting the output of urine to 1,500 cubic centimeters a day.

PNEUMOCOCCIC MENINGITIS

This highly fatal disease can be favorably influenced by sulfanilamide, especially when sulfanilamide treatment is combined with (1) the use of

specific serum given intravenously, (2) the use of repeated spinal drainage, and (3) the injection of either small amounts of specific serum or autogenous serum into the subarachnoid space.

The pneumococcus is killed by intracellular digestion. This is facilitated and accelerated in the presence of specific antiserum and complement (normal human serum). Sulfanilamide does not kill pneumococci in large numbers, but it inhibits their rate of reproduction. The rationale for the combined use of sulfanilamide, specific serum, and autogenous serum is as follows: The sulfanilamide inhibits the growth of the organisms, the specific serum provides antibody, and the autogenous serum provides antibody and complement. The reason it is necessary to inject specific serum and complement into the subarachnoid space is that antibody and complement diffuse into the subarachnoid space very slowly.

A study of the fatal cases of pneumococcic meningitis which have been treated with sulfanilamide shows that bacteremia, the presence of endocarditis or brain abscess, or injury to the brain, such as follows a fracture to the skull, all contribute to death.

The plan of treatment, as developed by Finland, Brown, and Rauh,[8] would appear to be the best for the present. It is the one that we have followed and may be summarized in this manner:

Sulfanilamide by mouth so that the concentration in the blood and spinal fluid is at least 10 milligrams per 100 cubic centimeters or more.

Repeated spinal drainage at least every twelve hours. All of the fluid should be drained off. Fluids should be administered freely in order to prevent dehydration and to insure a free flow of spinal fluid.

Specific antipneumococcic serum should be given intravenously to all patients with bacteremia, or to all patients who fail to show antibodies in the blood by means of slide agglutination with the same type of pneumococcus causing the meningitis.

Small amounts of antipneumococcic horse or rabbit serum (2 to 5 cubic centimeters), together with 15 to 20 cubic centimeters of fresh human serum, should be injected into the subarachnoid space daily until the spinal fluid is sterile.

Blood transfusions should be given repeatedly, especially when signs of anemia develop.

When specific antiserum is not available or the type of pneumococcus is not known, the patient's own blood serum, without added antibody, may be used, provided there is no bacteremia.

All patients with meningitis, regardless of its cause, should be started on sulfanilamide or sulfapyridin as soon as the diagnosis is made. The etiological diagnosis should then be established as quickly as possible.

It is important to use only small amounts of foreign protein intraspinally, since large amounts may be followed by a response with a thick purulent exudate.

PNEUMOCOCCIC PNEUMONIA

On the whole, the use of sulfanilamide in the treatment of pneumococcic pneumonia has not been very impressive. Finland and Brown,[9] of our clinic at the Boston City Hospital, have reported results in the treatment of Type III pneumonia with sulfanilamide or specific serum, or with a combination of these two agents. When reviewed from the point of view of the fatality rates, the results of treatment were not very striking. There were isolated instances in which this form of treatment was followed by definite improvement, and the bacteriological and immunological studies indicated that sulfanilamide and serum can alter the course of Type III pneumonia. These observations receive support from the experiments of Enders and his associates,[10] who have been able to show that sulfanilamide influences in a favorable way the Type III pneumococcic skin infections in rabbits. It was found that recovery occurred when the animal survived long enough to develop specific antibodies. A recent study of the action of sulfanilamide in pneumonia due to different types has been recorded by Price and Myers,[11] and suggests that the drug may have a favorable effect in some cases due to other types besides Type III. They report a fatality rate of 15.7 per cent for the sulfanilamide-treated cases. When the results with sulfanilamide were compared with the results of specific serum-treated cases of Types I, II, V, VII, and VIII pneumonia, the death rate in the sulfanilamide-treated cases was 10.5 per cent, and in the serum-treated cases was 27.5 per cent. This is what might be anticipated in this small group, since the incidence of bacteremia in the serum-treated group was 30 per cent, whereas in the sulfanilamide-treated group it was only 16 per cent.

From *in vitro* experimental studies of the action of sulfanilamide on the pneumococcus with and without the addition of specific serum, it would appear that the combination of both agents would be better than either one alone. This is probably the method that should be used in the treatment of pneumonia if sulfanilamide is used.

SULFAPYRIDIN IN PNEUMOCOCCIC INFECTIONS

In view of the slight effect of sulfanilamide in pneumococcic infections when used alone, one of the derivatives of sulfanilamide (sulfapyridin) has been introduced for the treatment of pneumococcic pneumonia[11] as well as other pneumococcic infections.[12] This drug has received wide publicity in the lay press, so that it is well to review some of the salient points concerning its use in the treatment of pneumonia. At the outset, it can be said with some degree of confidence that the numbers of cases of pneumonia that have been treated so far are too few to afford a safe basis for any final conclusions as to the effectiveness of this drug under different conditions, or the extent of its toxic effects. The available evidence at present clearly suggests that it has a definite place in the treatment of pneumonia. Any statements that are made concerning its value, however, are purely tentative, since all of the factors influencing the fatality rate, the duration and course of the disease following sulfapyridin have not been adequately appraised.

From studies of the action of sulfapyridin *in vitro*, it has been ascertained that the drug is bacteriostatic as well as bactericidal for large numbers of pneumococci of Types I, II, III, V, VII, and VIII. To accomplish maximum results, it is desirable to use a concentration of at least 5 to 7 milligrams per 100 cubic centimeters. There are

slight differences with various specific types, depending upon the methods employed for study, the concentration of the drug, and the media that is used.

In mice infected with pneumococci at the same time that treatment is started, death is often delayed in Type III infections until the treatment is discontinued; then the animal very often dies. With Type I and Type II infections, treatment with the drug prevents death of significant numbers of animals when inocula of 10,000 to 100,000 pneumococci are used. These studies indicate that the drug has both a bacteriostatic and a bactericidal reaction on the common types of pneumococcic infections.

Before discussing the use of sulfapyridin in the treatment of pneumonia,* one may well review some of the factors concerned in the prognosis of this disease, and also the results which can be obtained with the use of specific serum.

(To be continued)

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* For collateral comments on the use of sulfapyridin in the treatment of pneumonia, see in this issue, on page 143, under the caption, "Sulfanilamide and Sulfapyridin in the Treatment of Various Infections."

CONGENITAL MALFORMATIONS OF THE RECTUM AND ANUS: THEIR SURGICAL TREATMENT*

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CONGENITAL anomalies of the anus and rectum, although not common, are of sufficient importance to justify consideration and critical review at frequent intervals. They are said to occur about once in every five thousand and six thousand newly born infants, but accurate statistics are not available. During the past four years, six such cases have been seen on the Stanford surgical service, five of them having been referred from other parts of the State.

EMBRYOLOGY

The embryological development pertinent to these anomalies occurs between the fifth and ninth weeks. Excellent descriptions of the normal development have been given by Arey,[1] Hunter,[5] Johnson,[6] Keith,[7] Koff,[8] Lewis,[10] Pohlman,[12] Stieda,[13] Wood-Jones[15] and others, but the process might be summarized as follows: In a 5-millimeter embryo the cloaca exists as a terminal sac common to the intestinal tract and the allantois. It is a rather narrow cavity compressed from side to side, and is sharply angulated ventrally. Near this ventral angle the cloaca comes in contact and fuses with the ectoderm of the body surface to form the cloacal membrane. Soon a longitudinal division of the cloaca is accomplished by the down-growth of a single, wedge-shaped mesodermic fold, called the urorectal septum, separating it into a dorsal or rectal portion and a ventral urogenital sinus. If this connective tissue septum is not complete there remains a narrow cloacal duct. Normally, however, all communication between the urogenital sinus and the intestine is closed off by the end of the seventh week. The urorectal septum also divides the cloacal membrane into two segments, a urogenital membrane and an anal membrane. Later both membranes are broken through independently, forming a urogenital and an anal opening. When the edges of the ectoderm close in the perineal region so as to form a median raphe, a permanent perineum is produced. A small inpocketing from the perineum, called the proctodeum, forms the anal pit. This inpocketing continues until the proctodeum and rectum join their lumina, forming the anus and anal canal. (Figure 1.) The external anal sphincter muscle develops from regional mesenchyma independently from the bowel.

The urogenital sinus continues its development into the bladder, urethra and the genital tract. The Muellerian ducts, one on either side of the body, are formed as paths for the products of the reproductive glands. They obtain complete development only in the female, and undergo degeneration in the male embryo. They grow downward close together in this region, and extend horizontally on the wall of the urogenital sinus, opening into it later. In both

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